

REMARKS**STATUS OF THE CLAIMS**

Claims 1, 5-15, 20-39 and 41-207 were pending in this application. Claims 8, 167, 171, and 172 are canceled without prejudice. Claims 1, 25, 166, and 205 are amended. New claims 208-213 are added. Following entry of the amendments claims 1, 5-7, 9-15, 20-39, 166, 168-170, and 173-213 will be pending and at issue.

SUPPORT FOR AMENDMENTS TO THE CLAIMS

Claim 1 and 166 are amended to remove the process limitation and instead more clearly define Applicants' invention in purely structural terms by reciting that the "insulator comprises a channel between said first electrode and said second electrode..." (Claim 1) and by reciting "a channel within said insulating substrate, said channel having walls formed by said first electrode and said second electrode in said first electrode pair." (Claim 166) Support for these amendments can be found throughout the specification as filed, e.g., paragraphs 76-78, 191, Figs. 4A, 5, and 6A-6C. In addition, Claims 1 and 166 are amended to recite that "said first electrode and said second electrode are separated by less than 30 nanometers" and new claims 208-213 are added to recite electrode separations that are less than 20 nanometers (Claims 208 and 211) less than 15 nanometers (Claims 209 and 212) and less than 10 nanometers (Claims 210 and 213). Support for these amendments also can be found throughout the specification as filed, e.g., paragraphs 12 and 70. Claims 1 and 166 also are amended to recite that "said apparatus is configured to permit the formation of a plurality of independent, electrically coupled binding agent/analyte complexes between said first electrode and said second electrode ..." Support for this claim amendment can be found throughout the specification as filed, e.g., paragraphs 30, 54 – 58, 63, and 69.

Claim 25 is amended to correct inadvertent and/or typographical errors.

The amendments to the claims and the new claims therefore add no new matter.

REJECTIONS UNDER 35 U.S.C. § 112 – SECOND PARAGRAPH

Claim 25 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants appreciate the Examiner's careful reading of the claim and have removed the ambiguity by amending Claim 25 to correct a typographic error and so change the phrase "said as least" to "said at least." Withdrawal of this basis for rejection is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 102

Claims 1, 5-7, 11, 20-24, 166, 167, 171, 173, 174, 183, 192, 205 and 206 are rejected under 35 U.S.C. § 102(b) as allegedly being unpatentable over Ueda et al. (Japanese J. Appl. Phys. Pt. 1 (1999) 38(4A):2118-2119. Applicants traverse this ground of rejection by amendment and argument.

For a reference to anticipate an invention, the reference must teach each and every element of the claimed invention. Because Claim 1 as currently amended indicates that the "insulator comprises a channel..." and Claim 166 as currently amended indicates that there is "a channel within said insulating substrate..." these amendments distinguish these claims and their dependents from Ueda et al., as the Ueda et al. reference teaches "[a] pair of Al electrodes with a microgap (approximately 80 μ m) was fabricated onto a glass plate." Ueda et al. at 2118. Because Ueda fails to teach or suggest a channel within the glass (i.e., the insulator or insulating substrate), does not anticipate the claimed invention. Ueda et al. also fails to anticipate independent Claims 1 and 166 and their dependents because it discloses an 80 μ m spacing between the electrodes, and so fails to teach or suggest the limitation added by this amendment that "said first electrode and said second electrode are separated by less than 30 nanometers." Withdrawal of this basis for rejection is respectfully requested.

Claims 1, 5-7, 9-13, 20-31, 34-39, 166-171, 173-176, 179, 181, 183-189, 191-201, 203 and 205-207 are rejected under 35 U.S.C. 102(b) and (e) as allegedly being unpatentable by Eichen et al (US 2003/0203394A1 and Eichen WO 99/57550). For reasons identical to those set

forth in the preceding paragraph, Eichen et al. and Eichen also fail to anticipate the Claims 1 and 166 and their dependents as currently amended. The Eichen references teach that the electrodes are formed on a glass plate and so fail to teach or suggest the limitations that the “insulator comprises a channel...” (Claim 1) or “a channel within said insulating substrate” (Claim 166). The Eichen references teach a microgap of 12 micrometers, and so fail to teach or suggest or the limitation present in Claims 1 and 166 that “said first electrode and said second electrode are separated by less than 30 nanometers.” Withdrawal of this basis for rejection is respectfully requested.

In addition, Applicants traverse the rejection based on the Eichen references of Claims 37-39, and 194-196. Applicants respectfully submit that the cited sections of Eichen (paragraphs 0155, 0211, and 0300 of the US 2003/0203394A1 publication) do not teach or suggest the limitation present in these claims that the “electrode comprises a semiconductor material” but rather teaches that “... semiconductor particles ... may also be deposited on the nucleic acid sequences...” to “form[] a conductive bridge between the electrodes.” *Id.* Accordingly, withdrawal of this basis for rejection also is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 8 and 172 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Eichen (WO 99/57550) as applied to claims 1, 5-7, 9-13, 20-31, 34-39, 166-171, 173-176, 179, 181, 183-189, 191-201, 203 and 205-207. The Examiner has argued that Eichen et al. does not expressly teach separations of less than 70 Angstroms, but that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to optimize the method of Eichen with regard to the separation distance, pointing to Eichen’s statement that “Electrodes 300 are spaced from one another at a distance which should not exceed the combined length of the target DNA sequences 310 and the recognition moieties 306 and 308” citing Eichen at page 10, paragraph 0152. *See* Office Action at page 11. In addition, the Examiner points to *In re Aller*, 105 USPQ 233 at 235 for the proposition that it is routine experimentation and not inventive to discover optimum or workable ranges where general conditions of a claim are

discovered in the prior art. Against this background, Applicants traverse this ground of rejection by amendment and argument.

The instantly claimed invention as set forth currently amended Claims 1 and 166 is based on a discovery by Applicants of a combination of elements and geometries that produce biosensors capable of generating robust electrical signals with binding agents and analyte complexes such as, e.g., nucleic acids, without need or use of additional reagents to render the complex conductive. None of the cited references alone or in combination provide these advantages of the claimed invention.

Three requirements must be met for a *prima facie* case of obviousness. First, the prior art references must teach all the limitations of the claims. Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention. Third, a reasonable expectation of success is required.

The cited Eichen reference does not teach all of the elements of the claims. First, the reference fails to teach or suggest the channel limitation. *See* preceding section of response directed to the 102 rejections. Without wishing to be bound by theory, Applicants believe that the presence of a channel within the insulator acts to increase the signal to noise ratio of the claimed apparatus by at least one of the following mechanisms:

- 1) The overall electrical leakage pathway length is increased.
- 2) The number of electrical leakage pathways is reduced.
- 3) The number of locations for pinholes, through which electrical leakage or shorts could occur within the insulator, is reduced.

Applicants believe that these mechanisms apply to the insulator between (and in close proximity to) the electrodes that comprise an electrode pair and produce a concomitant reduction in the electrical noise of the claimed apparatus. Eichen does not teach or suggest the "channel" limitation or the advantages it provides.

Next, as the Examiner points out, the cited Eichen reference fails to teach or suggest the distance limitations recited in claims 1 and 166 as amended, or the distance limitations set forth

in dependent claims 8 and 172, or the limitations set forth in new claims 208 – 213. Applicants respectfully disagree with the Examiner's suggestion that the claimed distance limitations are the result of routine experimentation to discover optimum or workable ranges. Eichen's invention is directed to biosensors that rely on growth of a conductive [conducting] bridge or a conductive polymer nucleated on the binding agent to generate an electrical signal. *See, e.g.*, Abstract, Fig. 10B, Fig. 12 A, Fig. 30, paragraphs [0020] and [0021]. In contrast, the invention as claimed has distance limitations that enable the unexpected result of allowing a binding agent/analyte complex to be detected without the growth of a conductive [conducting] bridge or a conductive polymer as described in the instant specification, at, e.g., paragraphs [0194] through [0200].

One of skill in the art would have had no expectation of success. Assuming that the Eichen reference did teach or suggest all the claim elements (and Applicants do not concede that it does), one of skill in the art would have had no expectation of success when combining the elements of arriving at a molecular sensing apparatus capable detecting a binding agent/analyte complex such as, e.g., a double stranded nucleic acid without the use of exogenous agents to generate conductivity (in contrast to the methods taught by Eichen; *see also* Braun publication (from Eichen's group, submitted with supplemental information disclosure statement accompanying this amendment & response) *Nature* 391 (19 Feb. 1998): 775-777 at, e.g., Fig. 4 b bottom inset showing no current in the absence of silver deposition onto the DNA.) This conclusion reflects the uncertainty surrounding issues such as the conductivity of nucleic acid as described in Fink (Cell Mol. Life Sci. 58 (2001):1-3, *see, e.g.*, final paragraph on page 3, submitted with supplemental information disclosure statement accompanying this amendment & response), and the attached review by Richter (Physica E 16 (2003):157-159, *see, e.g.*, section 2 titled "conductivity of native DNA" starting on page 158, submitted with supplemental information disclosure statement accompanying this amendment & response).

With respect to the remaining obviousness rejections (i.e., of dependent Claims 14, 15, 177, 178, 180, 182, 202 and 204 as allegedly being unpatentable over Eichen (WO 99/57550) as applied to Claims 1, 5-13, 20-31, 34-39, 166-171, 173-176, 179, 181, 183-189, 191-201, 203,

and 205-207 in view of Eckhardt et al. (U.S. Patent 6,127,127) and dependent Claims 32, 33, and 190 as allegedly being unpatentable over Eichen (WO 99/57550) as applied to Claims 1, 5-13, 20-31, 34-39, 166-171, 173-176, 179, 181, 183-189, 191-201, 203 and 205-207 in view of Kovacs et al. (5,965,452)), Applicants respectfully submit that the secondary references (Eckhardt and Kovacs et al.) fail to supply the deficiencies of Eichen set forth above.

Consequently, a prima facie case of obviousness is not made. Withdrawal of these grounds of rejection of Claims 14, 15, 177, 178, 180, 182, 202 and 204 and of Claims 32, 33, and 190 is respectfully requested.

CONCLUSION

Withdrawal of the pending rejections and reconsideration of the claims are respectfully requested, and a notice of allowance is earnestly solicited. If the Examiner has any questions concerning this Response, the Examiner is invited to telephone Applicants' representative at (415) 875-2413.

Respectfully submitted,
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